Quantitation of Aortic Regurgitation by Computer Analysis of Digital Subtraction Angiography

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Digital subtraction angiography provides the potential to determine aortic regurgitant fraction by computer analysis of time-intensity curves generated from regions of interest positioned over the aorta and left ventricle after aortography. To validate this ability, we studied six dogs instrumented with an electromagnetic flow probe on the ascending aorta. Aortic regurgitation of varying severity was produced by a basket catheter introduced through the right carotid artery. Aortograms were performed using continuous fluoroscopy at 30 frames/s and stored in digital format in a 256 x 256 pixel matrix.

An image-processing computer was utilized to plot summated pixel intensity versus time for both the aortic and the left ventricular regions of interest. Regurgitant fraction was calculated from the time-intensity curves using an algorithm analogous to that employed by dye-dilution methods. Regurgitant fraction determined from digital angiography was compared with that obtained by electromagnetic flow and was found to correlate well (r = 0.94, SEE = 7.4%) over a wide range of values. Thus, these data indicate that aortic regurgitant fraction can be accurately determined from computer analysis of digitally acquired aortograms in an animal model of acute aortic regurgitation.

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The traditional assessment of the severity of aortic regurgitation by visual grading of aortic root angiograms is subjective and may be influenced by several factors, including left ventricular volume, radiographic technique, amount of contrast medium injected and inter- and intraobserver variability (1,2). Regurgitant fraction, calculated in the catheterization laboratory by comparison of angiographic with Fick or thermodilution-determined cardiac output, offers a more quantitative measurement of aortic insufficiency (3). This method, however, has a limited correlation with regurgitant fraction measured by electromagnetic flow methods in patients undergoing open heart surgery (4). Further, such calculations are greatly influenced by the presence of concomitant mitral regurgitation. Noninvasive estimates of aortic regurgitant fraction by gated blood pool scintigraphy (5-7) or Doppler echocardiography (8-10) suffer from similar technical limitations and have not achieved wide clinical acceptance.

Dye-dilution techniques have been used to measure aortic regurgitation in experimental settings, and the results have been shown to correlate closely with electromagnetic flow probe determinations (11-13). Previous investigators (14,15) have applied dye-dilution principles to videodensitometric analysis of cineaortograms to quantitate aortic regurgitation. Accordingly, we hypothesized that the regurgitant fraction in patients with aortic insufficiency could be accurately determined by computerized densitometric analysis of digital subtraction aortography.

Methods

Theoretical considerations. It has been previously demonstrated (11-13) that aortic regurgitant fraction can be calculated from dye-dilution curves after injection of indocyanine green into the aortic root. Using these methods, regurgitant fraction (RF) is determined by the formula

$$RF = \frac{\int C_{LV}dt}{\int C_{Ao}dt}$$

where $C_{LV}$ and $C_{Ao}$ = the concentration of indocyanine green measured in the left ventricle and aorta, respectively,
and \( \int C_{LV} \, dt \) and \( \int C_{Ao} \, dt \) are determined by planimetric measurement of the area under the respective time-concentration curves. We sought to apply this formula to digital aortography utilizing iodinated contrast medium as the indicator. Time-intensity curves can be easily generated from digital subtraction angiograms and have been used to measure blood flow in the coronary and systemic circulations (16–19). The area under a time-intensity curve represents mass of contrast medium rather than concentration. Because concentration = mass \times volume, concentration can be determined from a time-intensity curve by dividing the area under the curve by the volume of its region of interest. Therefore, we hypothesized that aortic regurgitant fraction could be determined from regions of interest positioned over the aorta and left ventricle after digital subtraction aortography by the formula

\[
RF = \frac{A_{LV}/V_{LV}}{A_{Ao}/V_{Ao}},
\]

where \( A_{LV} \) and \( A_{Ao} \) = the areas under the left ventricular and aortic time-intensity curves, and \( V_{LV} \) and \( V_{Ao} \) = the volumes of the left ventricular and aortic regions of interest, respectively.

**Animal preparation.** An open chest canine model of acute aortic regurgitation was used. Six dogs weighing 17 to 38 kg were pretreated with morphine sulfate (3 mg/kg body weight) and were anesthetized with alpha-chloralose urethane. The animals were intubated and mechanically ventilated with room air. A left thoracotomy was performed, and an appropriately sized electromagnetic flow probe (Zepeda Instruments) was positioned on the ascending aorta approximately 3 to 4 cm above the aortic valve plane. Stainless steel needle electrodes were attached to the skin to obtain a high quality electrocardiogram. The right carotid artery and both femoral arteries were surgically isolated for placement of several intravascular catheters, all of which were positioned under fluoroscopic guidance. A 5F micromanometer-tipped catheter (Millar Instruments) was positioned in the thoracic aorta to monitor aortic pressure, and a 6F NIH catheter was placed in the ascending aorta for the performance of aortography. The right internal jugular vein was utilized for insertion of a 7F Swan-Ganz catheter (American Edwards), which was positioned in the pulmonary artery for cardiac output measurements. The electromagnetic flow signal, central aortic pressure and electrocardiogram were continuously monitored utilizing a multichannel physiologic recorder (Gould Electronics).

**Induction of aortic regurgitation.** Aortic regurgitation was produced by a nonmetallic basket catheter similar in design to that used by Falsetti et al (20). A central stylet attached to the distal tip enabled incremental expansion of this catheter such that varying degrees of aortic regurgitation could be produced. For each dog, simultaneous aortography and electromagnetic flow recordings (50 mm/s paper speed) were obtained in the control state and during each level of acute aortic regurgitation.

**Electromagnetic flow data.** In vivo calibration of the electromagnetic flow signal was performed in the control state by comparing thermodilution cardiac outputs with simultaneously recorded electromagnetic flow signals. The Swan-Ganz catheter was then removed so as not to be in the radiographic field during aortography. End-diastolic flow in the control state was assumed to be zero; thus the flow signal corresponding to the onset of the electrocardiographic R wave was considered to represent the zero line. The zero line was established before and after each grade of aortic insufficiency by withdrawing the basket catheter above the aortic valve. The analysis of the electromagnetic flow tracings is shown in Figure 1. The area encompassed by the positive systolic deflection of the electromagnetic flow signal and the zero line was considered to represent total forward flow. The area encompassed by the negative diastolic deflection and the zero line was considered to represent regurgitant flow (including diastolic coronary flow). These areas were determined by planimetry of the flow signals of five consecutive cardiac cycles using a digitizing tablet and microcomputer (Cardio 80, Kontron Electronics). Aortic regurgitant fraction was calculated as the area representing regurgitant flow divided by the area representing forward flow as described by Malooy et al. (11).
Image acquisition. Under fluoroscopic guidance, the 6F NIH catheter was positioned 2 to 4 cm above the coronary cusps according to standard criteria (21). Aortography was performed by R wave-triggered power injection of diatrizoate meglumine (Hypaque 76, Winthrop) at 9 cc/s for 2 seconds. Images were obtained by continuous fluoroscopy (30 frames/s) at 24 mA and 70 to 85 kV. In each case the radiographic technique was adjusted to avoid saturation while utilizing the full dynamic range of the computer. The images underwent real-time analog to digital conversion into a 256 × 256 pixel matrix with an 8 bit gray scale capable of displaying 256 levels of gray. All images were stored in digital format on 10 megabyte high density floppy disks (Omega) for subsequent processing and analysis.

Analysis of the digital subtraction aortograms was accomplished by transferring the digital images to a dedicated medical image processing computer (MIPRON I, Kontron Electronics). All images underwent logarithmic transformation utilizing a look-up table to linearize the relation between contrast concentration and optical brightness (Beer-Lambert law). Digital subtraction was then performed for each image using a gated subtraction program that allowed each mask frame to be subtracted from the contrast-containing frame in the corresponding portion in the cardiac cycle. Aortic and left ventricular regions of interest were chosen on the basis of two considerations: 1) facilitation of reproducibility between observers, and 2) avoidance of excessive operator–computer interaction that might limit the practical application of this technique to the clinical setting. Accordingly, rectangular regions of interest were positioned over the aortic root and mid-left ventricle utilizing a custom-designed computer program. Size and angulation of the regions of interest were adjusted by the operator such that they were parallel to the long axis of the aorta and left ventricle, respectively, and completely encompassed the largest diameter of the chamber in which contrast was visualized. In addition, care was taken to avoid overlap of the aortic flow probe with the aortic regions of interest.

Time-intensity curves were generated for each region of interest by plotting summated pixel intensity versus time (Fig. 2). The area under each contrast time-intensity curve was determined by planimetry utilizing the same microcomputer and digitizing tablet utilized for electromagnetic flow measurement. This area was then converted from contrast intensity (or mass of contrast agent) to contrast concentration by dividing by the volume of the corresponding region of interest in pixels. This volume was calculated by assuming a circular cross section of both the aorta and the left ventricle such that volume = \pi (D/2)^2h where D = the diameter and h = the thickness of the region of interest measured in pixel units.

Regurgitant fraction due to aortic insufficiency can be calculated by the dye-dilution technique as the area under the left ventricular concentration-time curve divided by the area under the aortic concentration-time curve (11–13). Similarly, regurgitant fraction by digital subtraction aortography was determined as the contrast concentration of the left ventricular region of interest divided by the contrast concentration of the aortic region of interest.

Visual grading of aortography. Each aortogram was reviewed by two experienced observers. The amount of aortic regurgitation was determined by consensus opinion. The absence of aortic regurgitation was characterized by failure to visualize contrast in the left ventricle after aortic root injection. The following grading scale was utilized to assess the severity of aortic regurgitation: mild, left ventricular contrast clearing with each cardiac cycle; moderate, left ventricular contrast not clearing with each cycle but of less intensity than contrast in the aortic root; and severe, left ventricular contrast intensity equal to or greater than that in the aortic root.

Statistical analysis. Linear regression analysis was used to compare regurgitant fraction obtained by digital angiography with that obtained by electromagnetic flow. Mean values of regurgitant fraction by electromagnetic flow were determined for each angiographic grade of aortic regurgi-

Figure 2. Calculation of regurgitant fraction from time-intensity curves generated from digital aortography. Left, A processed, subtracted digital image illustrating the position of the aortic (AO) and left ventricular (LV) regions of interest in a dog with severe aortic regurgitation. Right, Time-intensity curves from the aorta (top line) and left ventricle (bottom line). The area under each time-intensity curve is divided by the volume of its corresponding region of interest to obtain concentration of contrast agent within the region of interest. Regurgitant fraction is then calculated as left ventricular contrast concentration divided by aortic contrast concentration. DSA = digital subtraction angiography; EMF = electromagnetic flow.
tation and compared using Student's t test. Inter- and intraobserver variability was determined from blinded analysis of 10 digital aortograms 6 months after the initial study. Excellent agreement was present for both interobserver (r = 0.98, SEE = 4.2%) and intraobserver (r = 0.97, SEE = 6.7%) measurements.

**Results**

A total of 33 aortograms was performed in six dogs; three of the aortograms were lost because of technical difficulties with the digital storage media. In the remaining 30 studies, heart rate varied from 50 to 127 beats/min. One animal was given intravenous lidocaine to suppress frequent ventricular ectopic beats. Thermol dilution cardiac output ranged from 2.7 to 5.7 liters/min in the control state. During aortic regurgitation, forward output ranged from 2.9 to 8.3 liters/min.

**Regurgitant fraction by digital subtraction angiography.** Regurgitant fraction by electromagnetic flow ranged from 5.3 to 72.8% whereas regurgitant fraction by the digital subtraction method ranged from 2.4 to 78.2%. The regurgitant fraction obtained by digital subtraction aortography was compared with that obtained by electromagnetic flow by linear regression analysis (Fig. 3). The regression line approximated unity with a y intercept of 0.456 and a slope of 0.98. A close correlation was observed (r = 0.94) with a small SEE (7.4%) over a wide range of regurgitant fractions and heart rates.

**Visual grading of angiography.** A comparison was made between the assessment of the severity of aortic regurgitation by visual grading of angiograms and the regurgitant fraction by electromagnetic flow (Fig. 4). In the control state, regurgitant fraction by electromagnetic flow represents diastolic coronary flow and averaged 6.5 ± 0.9%. The mean values of regurgitant fraction for the various grades of aortic regurgitation were as follows: mild, 32.0 ± 11.6; moderate, 50.7 ± 14.5; severe, 65.0 ± 7.9. Although the mean values of regurgitant fraction were significantly different (p < 0.01) between groups, considerable overlap was present.

**Discussion**

Digital subtraction angiography has been previously used to grade the severity of aortic regurgitation. Booth et al. (22) reported that visual grading of digital subtraction aortography systematically overestimates the degree of aortic regurgitation determined with cineangiography. This was attributed to enhancement of myocardial contrast by digital subtraction. Klein et al. (23) evaluated a computer-generated index of aortic regurgitation by digital subtraction angiography and found that it correlated well with visual grading using a conventional semiquantitative scale. Our data establish that regurgitant fraction can be accurately quantified by digital subtraction aortography in an experimental model of acute aortic insufficiency. This technique offers a direct assessment of aortic regurgitant fraction rather than a comparison of aortic with pulmonary artery flow. In addition, this method is quantitative and is thus superior to subjective visual grading of aortic regurgitation.

**Accuracy and advantages.** Although previous investigators (14,15) successfully applied analog videodensitometry to cineangiography to quantitate aortic regurgitation, our method offers several technical advantages. Digital formatting facilitates analysis of images, is reproducible and...
avoids difficulties introduced by nonlinearity of film. The use of logarithmic transformation corrects for the nonlinear relation between contrast concentration and optical brightness. Gated subtraction minimizes or eliminates the contribution of background structures to contrast intensity. Because the final processed image represents contrast present in the aorta and left ventricle, contrast concentration can be derived by dividing contrast density by chamber volume.

Left ventricular chamber volume can be determined by the area–length method so that left ventricular contrast concentration could be assessed from a region of interest circumscribing the left ventricle as the contrast intensity within the left ventricle divided by left ventricular volume. If this were done frame by frame, a left ventricular concentration-time curve could be defined. However, this would require considerable operator–computer interaction and cumbersome mathematics. Therefore, we chose to use stationary regions of interest that were of sufficient size to avoid missing the regurgitant jet and could be reproducibly positioned by different observers. Importantly, the contrast concentration within a given region of interest does not necessarily reflect the contrast concentration within its respective cardiac chamber because of several factors, including contrast streaming, motion during the cardiac cycle, overlapping myocardial contrast and radiographic factors such as beam hardening artifact, scatter and veiling glare. Nevertheless, the regions of interest utilized in this experiment appear to be justified by the overall accuracy of the method as well as the excellent agreement among and between observers.

Limitations. A number of potential limitations exists for the calculation of aortic regurgitant fraction in this investigation. The effects of streaming or inadequate mixing of blood and contrast could lead to error in the time-intensity curves. We believe that this potential source of error was minimized by the use of a frequent sampling rate (30 frames/s) and broad regions of interest that encompassed the widest dimension of the aorta and left ventricle.

An important source of error inherent in this method is the contribution of myocardial contrast to the contrast time-intensity curves. The appearance of contrast in the myocardium after injection into the aortic root reflects coronary flow and tends to overestimate regurgitant fraction. This effect tends to be greater in mild aortic regurgitation in which myocardial contrast provides a relatively greater proportion of the total contrast intensity in the left ventricular region of interest. In contrast, severe aortic insufficiency results in a large volume of contrast in the left ventricle such that the contribution of myocardial contrast to total intensity is less. Further, the effect of myocardial contrast in acute severe aortic regurgitation would be minimized by the associated reduction in total coronary flow and a shift from diastolic to systolic coronary flow (20,24,25). In this study, the ‘‘regurgitant fraction’’ determined by digital subtraction aortography in the control state theoretically represents myocardial contrast due to coronary flow and averaged 5.2% with a range of 2.4 to 8.3%. Thus, the error introduced by myocardial contrast appears to be minimal.

In this investigation, we studied acute aortic regurgitation in an experimental animal preparation. It is uncertain how completely these results may be extrapolated to chronic aortic regurgitation in humans. In particular, the geometric assumption of a circular cross section of the left ventricular region of interest may be less accurate in the presence of chronic aortic regurgitation with a dilated left ventricle. To test the dependence of the method on geometric assumptions, we introduced a known error of ±15% into the calculated volume of the left ventricular region of interest. This resulted in an average change in regurgitant fraction of 6.7%, suggesting that the method is relatively independent of minor errors in the determination of the volume of the left ventricular region of interest.

Finally, the determination of regurgitant fraction by the digital subtraction method could theoretically be affected by variations in heart rate. To assess the effect of heart rate on this technique, we plotted the error of the method as assessed by the difference between the regurgitant fractions obtained by digital subtraction and electromagnetic flow versus heart rate. A scattergram was observed (r = 0.02) suggesting that the method is independent of heart rate.

Clinical application. Despite these limitations, we believe that regurgitant fraction determined from digital aortography may be a better reference standard than traditional cineangiography for assessing the severity of aortic regurgitation. As such, it may be useful in evaluating the ability of other methods, particularly noninvasive techniques such as Doppler ultrasound or radionuclide imaging, to predict the magnitude of aortic regurgitation. Further, it may provide a method for determining whether the effect of afterload reduction or inotropic stimulation on regurgitant fraction is useful in evaluating left ventricular contractile reserve.

Conclusion. This study demonstrates that aortic regurgitant fraction can be accurately quantified by analysis of time-intensity curves generated from the aorta and left ventricle after digital subtraction aortography. This method appears to be superior to conventional semiquantitative measurements of aortic regurgitation and thus may be useful in the clinical assessment of this disorder.

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References


